## *Remarks*

Reconsideration of this Application is respectfully requested. Pursuant to 37 C.F.R. § 1.116(a), Applicants respectfully request entry of this Amendment and Reply after a Final Office Action because it is accompanied by a Request for Continued Examination in compliance with 37 C.F.R. § 1.114.

Upon entry of the foregoing amendments, claims 63-71 are pending in the application, with claims 63 and 70 being the independent claims. Claims 1-40 and 42-51 were previously cancelled. Claims 41 and 52-62 are presently cancelled without prejudice to or disclaimer of the subject matter therein.

New claims 63-71 are sought to be added. Support for new claims 63-71 can be found, *inter alia*, as provided in Table 1 of the Supplemental Amendment dated December 22, 2003; page 10 of the Amendment and Reply Under 37 C.F.R. § 1.111 dated January 12, 2006; and at page 43, lines 1-10; page 18, lines 10-29; page 41, lines 11-29; and Section IV.K., pages 41-42 of the specification.

The title is sought to be amended in view of the present claims. The specification is also sought to be amended to correct a typographical error in a related application number and to update the status of the applications recited in the Cross-References to Related Applications.

As such, the amendments to the claims and specification are believed to add no new matter and their entry is respectfully requested.

***Previously Withdrawn Claims***

Prior claims 54, 56, and 59 were withdrawn by the Examiner in the Office Action dated July 12, 2005 and claim 60 was withdrawn by the Examiner in the Final Office Action dated July 26, 2007. In the event that the Examiner considers the prior Election of Species Requirements applicable to the present claims, Applicants incorporate herein their prior provisional elections and/or traversals of August 2, 2004 and May 4, 2006 in an effort to advance prosecution. Applicants reassert the right to claim additional species in the event that a generic claim is found to be allowable in accordance with 37 C.F.R. § 1.141(a).

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

***Rejection Under 35 U.S.C. § 112, First Paragraph - Written Description***

The Examiner rejected claims 52, 55, 57, 58, 61 and 62 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. *See* Office Action at pages 2-5. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 52, 55, 57, 58, 61 and 62, rendering the Examiner's rejection in regard to these claims moot. Applicants will address the Examiner's rejection in the event the Examiner finds it applicable to the present claims.

***Legal Principles***

The test for the written description requirement is whether one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Federal Circuit has re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed.'" *Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000). Furthermore, an Applicant is not required to explicitly describe the subject matter. *Unocal*, 208 F.3d at 1000; *see also* M.P.E.P. § 2163.02 ("The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba* in order for the disclosure to satisfy the description requirement.").

***Prior claim 52***

The Examiner alleges that "[t]here is no support in the specification as originally filed for the composition of claim 52." Office Action at page 2. Applicants respectfully disagree for the reasons of record, and also for the reason that the compositions disclosed in the specification include compositions for use in diagnostic *in vitro* assays to evaluate recall responses (*see, e.g.*, page 18, lines 18-29; page 41, lines 11-19; and Example 16) which do not require a carrier.

However, solely to advance prosecution and not in acquiescence to the Examiner's rejection, Applicants have canceled claim 52, rendering the Examiner's rejection in regard to this claim moot.

At page 2 of the Office Action, the Examiner states "the specification discloses vaccines or pharmaceutical compositions containing a pharmaceutically acceptable carrier." In view of the Examiner's comments, it is Applicants' understanding that present claims 64 and 68, which recite a pharmaceutically acceptable carrier, fall within the scope of subject matter that the Examiner finds supported by the specification.

***Prior claim 55***

In regard to claim 55, the Examiner alleges that there is no support in the specification for the recitation of "wherein said one or more second peptides is a cytotoxic T cell (CTL)-inducing peptide or a helper T cell (HTL)-inducing peptide." Office Action at page 4. Applicants respectfully disagree for the reasons of record. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claim 55, rendering the Examiner's rejection in regard to this claim moot. Applicants will address the Examiner's rejection in the event the Examiner finds it applicable to the present claims.

As a preliminary matter, the Examiner appears to be of the opinion that the specification discloses only vaccine compositions. *See, e.g.*, Office Action at page 4. Applicants maintain that the vaccine compositions disclosed in the specification are only one of multiple embodiments of immunogenic compositions disclosed in the specification related to the peptides of the claims. For example, the specification provides compositions for use in peptide immunization of animals (*see, e.g.*, page 18,

lines 10-29); for use in diagnostic *in vitro* assays to evaluate recall responses (*see, e.g.*, page 18, lines 18-29; page 41, lines 11-19; and Example 16), as well as vaccine compositions for delivering immunogenic epitopes or peptides (*see, e.g.*, page 12, lines 26-31 and page 41, line 31 to page 46, line 6). As such, the specification clearly provides disclosure for multiple immunogenic compositions, of which vaccine compositions are one non-limiting embodiment. To further define the multiple compositions disclosed in the specification, Applicants have added new claims 64-71 directed to "immunogenic" compositions.

Applicants maintain that the specification supports the concept that multiple peptide epitopes, CTL and/or HTL, can be combined in the immunogenic compositions of the present claims. With regard to support for a CTL-inducing peptide or a HTL-inducing peptide, the specification provides in certain embodiments that

> An additional advantage of an epitope-based vaccine approach is the ability to combine selected epitopes (CTL and HTL), and further, to modify the composition of the epitopes, achieving, for example, enhanced immunogenicity.

Page 8, lines 12-14 of the specification.

Additionally, the specification discloses in certain embodiments that

> [A] polyepitopic peptide composition comprising multiple CTL and HTL epitopes that target greater than 98% of the population may be created for administration to individuals at risk for both HBV and HIV infection. The composition can be provided as a single polypeptide that incorporates the multiple epitopes from the various diseases-associated sources, *or can be administered as a composition comprising one or more discrete epitopes*.

Page 84, lines 27-32 of the specification (emphasis added). Thus, the specification clearly contemplates that a second epitope, can be a discrete CTL or HTL epitope.

Accordingly, a second epitope corresponding to either a CTL or HTL peptide is fully supported by the specification.

The Examiner states that "whilst the cited passages disclose vaccine compositions containing the components under consideration, the instant claims encompass nonvaccine compositions containing the aforementioned ingredients that are not disclosed in the specification." Office Action at page 4. Applicants note that the CTL and HTL epitopes, as described in the specification, are representative examples of CTL and HTL epitopes in general. Thus, the scope of the present claims is clearly supported by the specification.

***Prior claims 61 and 62 - "composition"***

The Examiner maintains that "[t]here is no support in the specification as originally filed for the composition of claims 61, 62." Office Action at page 4. In particular, the Examiner reiterates that the specification "discloses the peptide of claim 61/62 linked to a CTL epitope . . . but does not disclose the claimed composition which is not a vaccine and wherein the peptides are not linked." *Id.* Applicants respectfully disagree for the reasons of record.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 61 and 62, rendering the Examiner's rejection in regard to these claims moot. Applicants will address the Examiner's rejection in the event the Examiner finds it applicable to the present claims.

With respect to HTL peptides, the Examiner states that the passage previously cited by the Applicants refers to "'epitopes from the various disease associated sources' wherein the HTL peptides recited in the instant claims are not disease associated HTL."

Office Action at page 4. Applicants maintain that, in addition to disease associated HTL, the specification also describes other types of HTLs including "loosely restricted HLA-restricted" or "promiscuous" HTLs. *See, e.g.*, page 50, line 28 to page 51, line 12 of the specification. Representative examples of such "promiscuous" HTLs are also disclosed. *See id.* Applicants also note that HTL as recited, for example, in claims 66, 69 and 70, does in fact encompasses disease associated HTL. As such, any disease associated HTL described in the specification is a representative example of an HTL according to the claims.

Thus, the scope of the present claims is clearly supported by the specification.

***Prior claim 61 - "pan-DR-binding epitope"***

The Examiner maintains the rejection of claim 61, alleging that the "claims encompass a vast collection of artificial peptides with the functional attributes of a pan-DR binding epitope wherein the identity of said peptides is not disclosed in the specification and it appears unpredictable as to what peptides would or would have said functional attributes." Office Action at page 5. Applicants respectfully disagree for the reasons of record. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claim 61, rendering the Examiner's rejection in regard to this claim moot.

The Examiner did not reject prior claim 62 on the above-mentioned grounds related to claim 61. As such, it is Applicants' understanding that claim 69, which recites language similar to that of prior claim 62, falls within the scope of subject matter that the Examiner finds supported by the specification.

For at least the reasons above, Applicants therefore assert that the present claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

***Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement***

Claims 53 and 58 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. *See* Office Action at pages 7-11. Applicants respectfully disagree for the reasons of record. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 53 and 58, rendering the Examiner's rejection in regard to these claims moot. Applicants will address the Examiner's rejection in the event the Examiner finds it applicable to the present claims.

***Legal Principles***

In order for a claim to be enabled, the specification must teach one of ordinary skill in the art to make and use the invention without undue experimentation. The factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: (1) the guidance provided by the specification; (2) the amount of pertinent literature; (3) the presence of working examples; and (4) the predictability of the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.*

***The claims are not limited by a recited use, and the disclosed uses correlating with the present claims are enabling.***

As Applicants have noted previously, the Examiner's rejection is one based on "how to use." Applicants respectfully remind the Examiner that

> [W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire score of that claim is sufficient to preclude a rejection for nonenablement based on how to use . . . if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

M.P.E.P. § 2164.01(c).

The Examiner reiterates that "the claimed inventions are drawn to a pharmaceutical composition that can be used to treat/prevent HBV infection. The substantial/real life use for the claimed inventions are preventing and treating HBV infection in humans." Office Action at page 10. However, the Examiner's comments do not address Applicants' arguments that there is *no use limitation recited in the claims*. The Examiner simply states that there is an intended use limitation when, in fact, there is not. Applicants assert that the present claims are not limited by a recited use, so any enabled use disclosed in the specification enables the claims if the use is in keeping with their scope.

"As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims." M.P.E.P. § 2164.08 (2006) (citing *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003); *In re Moore*, 439 F.2d 1232, 1236 (C.C.P.A. 1971); *see also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003).

Without disclaiming or disparaging any of the uses disclosed by the specification, Applicants assert that the enablement requirement does not require data showing treatment efficacy or any clinical use as it would appear that the Examiner would require. As described above, the specification provides that the claimed immunogenic compositions can be used, for example, in peptide immunization of animals (*see, e.g.*, page 18, lines 10-29); in diagnostic *in vitro* assays to evaluate recall responses (*see, e.g.*, page 18, lines 18-29; page 41, lines 11-19; and Example 16); and in vaccine compositions for delivering immunogenic epitopes or peptides (*see, e.g.*, page 12, lines 26-31 and page 41, line 31 to page 46, line 6). Thus, Applicants have enabled the present claims for at least one use which correlates with the claimed invention.

"[A] specification disclosure which contains a teaching of the manner and process of making and using the invention . . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support." *Rasmusson v. Smithkline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (quoting *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971)). As discussed above, the application as filed provides an enabling disclosure of the present immunogenic compositions. At least with respect to the peptide immunization of animals and *in vitro* diagnostic assays, the Examiner has not provided any evidence that such uses would not be enabling.

***The enablement requirement does not require that the peptides of the claims bind most HLA alleles and elicit CTL in most individuals.***

At page 9 of the Office Action, the Examiner alleges that "the peptide recited in the claims does not bind most HLA alleles and therefore would not even elicit CTL in

most individuals." Without disclaiming or disparaging any of the properties disclosed by the specification, Applicants assert that the enablement requirement does not require that the claimed peptides bind most HLA alleles and elicit CTL in most individuals, for at least the reasons discussed above with regard to the use limitations alleged by the Examiner.

Even assuming that Applicants would have to enable an artificially created use limitation of the claims, Applicants note that the claimed immunogenic compositions are not limited to containing only a single peptide because the claims recite the open-ended language of "comprising." For example, the specification discloses methods for obtaining broad population immunogenicity, including combining the peptides of the present claims with other peptide epitopes that bind to other HLA alleles which, when considered in total, are present in most of the population. *See, e.g.*, page 31 of the specification. Table XXI lists the overall frequencies of the HLA class I supertypes in various ethnicities (Table XXIa) and the combined population coverage achieved by certain supertypes (Table XXIb). *See, e.g.*, page 31, lines 9-12 of the specification. Thus, Applicants have enabled the present claims for at least one use which correlates with the claimed invention.

As such, Applicants assert that a person having ordinary skill in the art, in view of the teachings of the specification and the knowledge in the art, would be able to provide for broad population coverage using the claimed peptides and methods described in the specification.

***The enablement requirement does not require clinical data of efficacy.***

The Examiner appears to allege that Applicants must demonstrate the clinical efficacy of the claimed subject matter to comply with the enablement requirement. *See, e.g.*, Office Action at page 11. Applicants again assert that there is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, description of *in vitro* and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use. To this end, the Federal Circuit has stated that:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

*Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995) (holding that animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph). Thus, even assuming that Applicants would have to enable an artificially created use limitation of the claims, Applicants note that the specification provides *in vitro*, as well as *in vivo* assays, as to how the peptides and compositions of the invention would be assayed, for example, for their immunogenicity using animals.

In view of the foregoing discussion, Applicants submit that a person having ordinary skill in the art, in view of the teachings of the specification and the knowledge in the art, would be able to make and practice the full scope of the present claims.

***The present claims are not limited to a single HBV peptide.***

In explaining the enablement rejection, the Examiner alleges "[t]here is currently no known pharmaceutical composition containing a single HBV peptide for treating or preventing HBV in humans." Office Action at page 9. As discussed above, the claimed immunogenic compositions are not limited to containing only a single peptide because the claims recite the open-ended language of "comprising." Accordingly, Applicants assert that the issue of whether or not compositions containing a single HBV peptide were known, has limited relevance to the enablement of the full scope of the present claims.

***Data supporting the use of the claimed peptides to treat HBV is available.***

The Examiner, in explaining another aspect of the enablement rejection, alleges that "[t]here is no evidence of record that intact polymerase (or the pol derived peptide recited in the claim) can be used to treat HBV infection in humans." Office Action at page 9. While Applicants do not agree that such evidence is necessary to enable the present claims, Applicants provide the Mizukoshi reference (Mizukoshi, E., *et al.*, *J. Immunol.* 173:5863-5871, 2004; Exhibit A) as confirmatory evidence of the therapeutic usefulness of HBV polymerase peptides, including an exemplary peptide recited in claims 63 and 70, to treat HBV infection in humans. In particular, Mizukoshi provides 10 CD4+ T cell epitopes within HBV polymerase that were used to analyze the immunological effects of long-term antiviral therapy as compared to spontaneous

recovery from HBV infection. *See* Mizukoshi at Abstract and Table I, Peptides 4-13. SEQ ID NO: 638 (recited in claim 63) corresponds to the nested MHC class I binding motif of Peptide 11 (*see* underlined portion of Peptide 11, Table I). The 10 HBV polymerase peptides exhibited high binding affinity to several HLA DR molecules (*see* Table II) and immunogenicity by IFN-γ ELISPOT assay in HBV-infected patients (*see* Figures 1 and 2). The nested sequences of certain HBV polymerase epitope peptides, including the peptide corresponding to SEQ ID NO: 638, were also sufficient to induce CD8+ T cell responses in HBV patients (*see* Figure 3B). Taken together, this evidence clearly demonstrates that HBV polymerase peptides, including an exemplary peptide recited in claims 63 and 70, are useful to treat HBV infection in humans and would allow coverage of a broad and ethnically diverse patient population.

Applicants remind the Examiner that a post-filing date reference setting forth data substantiating enablement "pertains to the accuracy of a statement already in the specification. ... It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)." *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995). Consequently, such evidence supports enablement of the claims under 35 U.S.C. § 112, first paragraph.

***Interpretation of prior claim 41***

At page 11 of the Office Action, the Examiner maintains that "[i]n view of previously pending claim 45, claim 41 is interpreted as encompassing the peptide recited in the claim attached to another peptide(s)." Applicants respectfully disagree for the reasons of record.

Solely to advance prosecution, and not in acquiescence to the Examiner's interpretation, Applicants have cancelled claims 41 and 52-62 and have presented a new claim set. With the cancellation of claims 41 and 45, the Examiner's previous interpretation of claim 41 is rendered moot. Claim 63 is directed to "[a]n isolated peptide at most 14 amino acid residues in length comprising an oligopeptide selected from the group consisting of: QAFTFSPTYK (SEQ ID NO:638); LVVDFSQFSR (SEQ ID NO:620); NVSIPWTHK (SEQ ID NO:625); and SAICSVVRR (SEQ ID NO:653)."

***Rejection Under 35 U.S.C. § 102***

Claims 41, 52, 53, 55, 57 and 58 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Seeger *et al.* (Seeger), U.S. Patent No. 5,360,714, as evidenced by Pasek *et al.* (Pasek). *See* Office Action at pages 12 and 13. Applicants respectfully disagree for the reasons of record.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 41, 52, 53, 55, 57 and 58, rendering the Examiner's rejection in regard to these claims moot. Applicants will address the Examiner's rejection in the event the Examiner finds it applicable to the present claims.

***Legal Principles***

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); M.P.E.P. § 2131. As stated by the Federal Circuit in *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996): "[t]o anticipate a claim, a reference must disclose

every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." The absence of any claimed element from the reference negates anticipation. *Minn. Mining & Mfg.*, 976 F.2d at 1572 (*citing Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1574 (Fed. Cir. 1984)).

Furthermore, if an independent claim is not fully met by an alleged prior art reference, neither are the more limited dependent claims. *See Application of Royka,* 490 F.2d 981, 983-984 (Cust. & Pat. App. 1974).

***Seeger does not disclose all of the limitations of the present claims and therefore does not anticipate the present claims.***

Independent claims 63 and 70 recite an isolated peptide *at most 14 amino acids in length*. Seeger does not disclose the exact peptide as recited in claims 63 and 70. Seeger only discloses a peptide sequence that *comprises* the claimed peptide. *See* Seeger, col. 10, 3rd paragraph, col. 5, 3rd paragraph, cols 11-12. As such, Seeger does not disclose all of the limitations of claims 63 and 70.

Claims 64-69 depend, either directly or indirectly, from claim 63, and therefore incorporate all of the limitations of claim 63. *See* 35 U.S.C. § 112, fourth paragraph. Claim 71 depends directly from claim 70, and therefore incorporates all of the limitations of claim 70. As discussed above, Seeger does not disclose the exact peptide as recited in claims 63 and 70. Dependent claims 64-69 and 71 incorporate the limitations of claims 63 and 70, respectively, and therefore, Seeger also does not disclose all of the limitations of claims 64-69 and 71.

Thus, for at least the reasons discussed above, Applicants assert that Seeger does not teach all of the limitations of claims 63-71. Consequently, Seeger does not anticipate the present claims.

## *Conclusion*

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Final Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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